

Comparison of Estimated PCB-153 Concentrations in Human Milk Using Various Pharmacokinetic Models

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Introduction

Background: Fish consumption can be a significant source of lipophilic contaminants, such as polychlorinated biphenyls (PCBs). These contaminants can concentrate in human milk resulting in the nursing infant being at the pinnacle of the human bioconcentration food chain. Risk to infants from consuming the milk of mothers who eat contaminated fish has not been quantitatively addressed in the fish advisory process. In the case of PCBs, EPA guidance for fish advisory programs uses the oral reference dose for Aroclor 1254 to establish the allowable fish consumption rate for children and adults who eat fish. This method does not account for the significant bioconcentration in the adipose of an expectant mother that will be mobilized and incorporated into breast milk. To adequately protect nursing infants, an especially vulnerable population, the nursing infant, this dose from milk consumption should be considered when developing fish advisories and assessing risk at sites where lipophilic contaminants are present. Obtaining human milk samples to measure contaminant concentrations is not practical in most cases, so it is desirable to have a method to estimate milk concentrations based on a lifetime average daily dose to the mother. Multiple models have been developed to produce these estimates. Our objective here was to evaluate the precision of disparate models to provide risk assessors and public health practitioners with the information they need to choose the most appropriate model. A secondary objective was to highlight the marked increase in dose that occurs between maternal lifetime intake and the nursing infant (See Fig. 5). To that end, we compared adaptations of 3 published models[1-4] as to their ability to predict human milk concentrations of PCB congener 153 (PCB-153) and doses to infants (Fig. 1-4), compared PCB-153 doses to mothers with estimated doses to infants (Fig. 5), and calculated the effect of maternal dietary interventions at various ages on subsequent PCB-153 concentrations in breast milk.

Methods: The Haddad model is an 8-compartment physiologically-based pharmacokinetic (PBPK) model that has been validated by comparing estimated milk concentrations against concentrations measured in a Canadian Inuit population[1]. The Yang model is a 3-compartment PBPK model[2], and the EPA model is a single compartment, first-order kinetic model[3,4]. We compared the models by using data from 8 individuals who breast fed for at least 11 months and represented a spread of average daily doses of the PCB congener 153 (PCB-153); these individuals were from the data on Canadian Inuits provided by Sami Haddad. Using the Haddad model, we also compared lifetime average maternal daily doses with average daily doses to infants during the nursing period (Fig. 5). Finally, using the Yang model, we calculated milk concentrations assuming dietary intervention, such as recognition and compliance with a fish advisory, at different life stages in the woman's life (Fig. 6).

Results: Simulated milk concentrations and doses to the infants from each of the 3 models for the selected individuals were similar within a factor of 2. EPA's model, the simplest, consistently calculated 1-year average milk concentrations that were the highest of the 3 models but still within a factor of 2 (See Figures 1-4) of the validated Haddad model. This suggests that the EPA model is accurate and protective and may be a good choice for risk assessors and fish advisory practitioners. We found that PCB-153 doses to the infant were, on average 2 orders of magnitude higher than the maternal lifetime daily average (Fig. 5). Figure 6 depicts the importance of early dietary intervention in a woman's life to prevent accumulation of PCB-153 that will later be passed on to the infant via nursing.

Comparison of Models

Figure 1

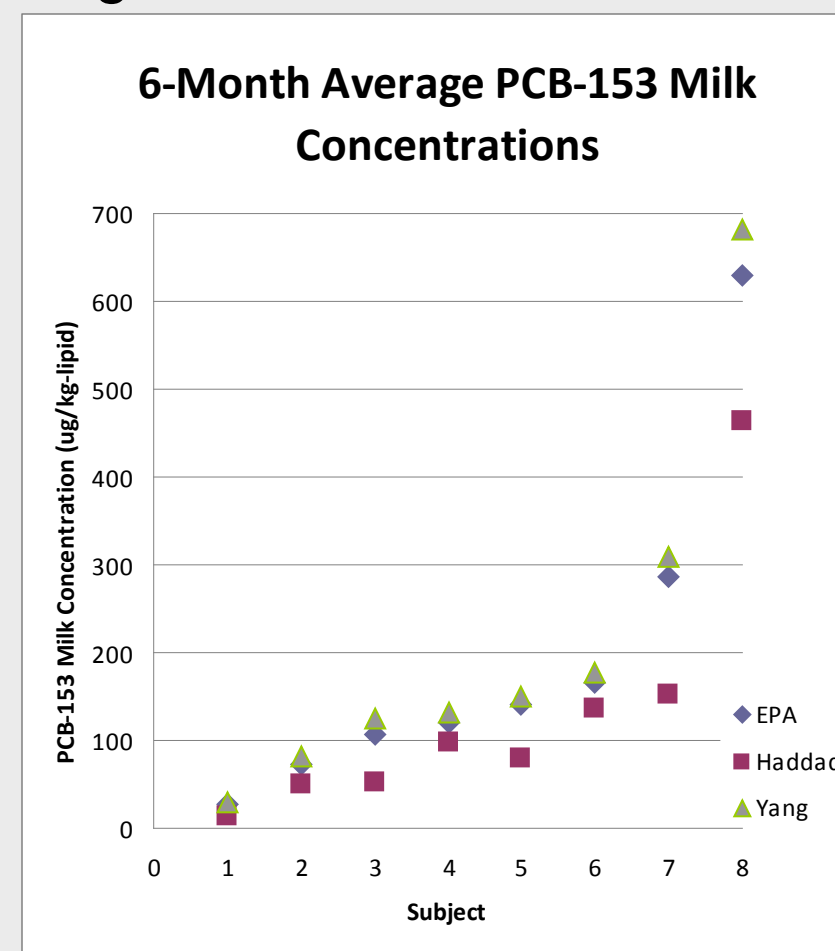


Figure 2

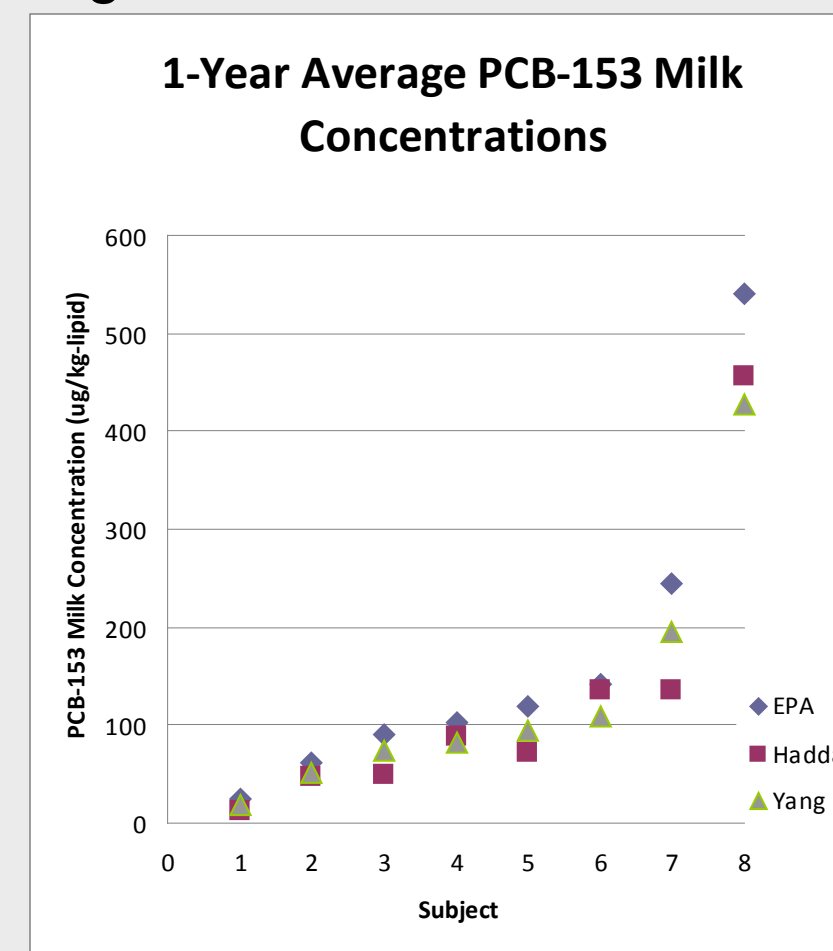


Figure 3

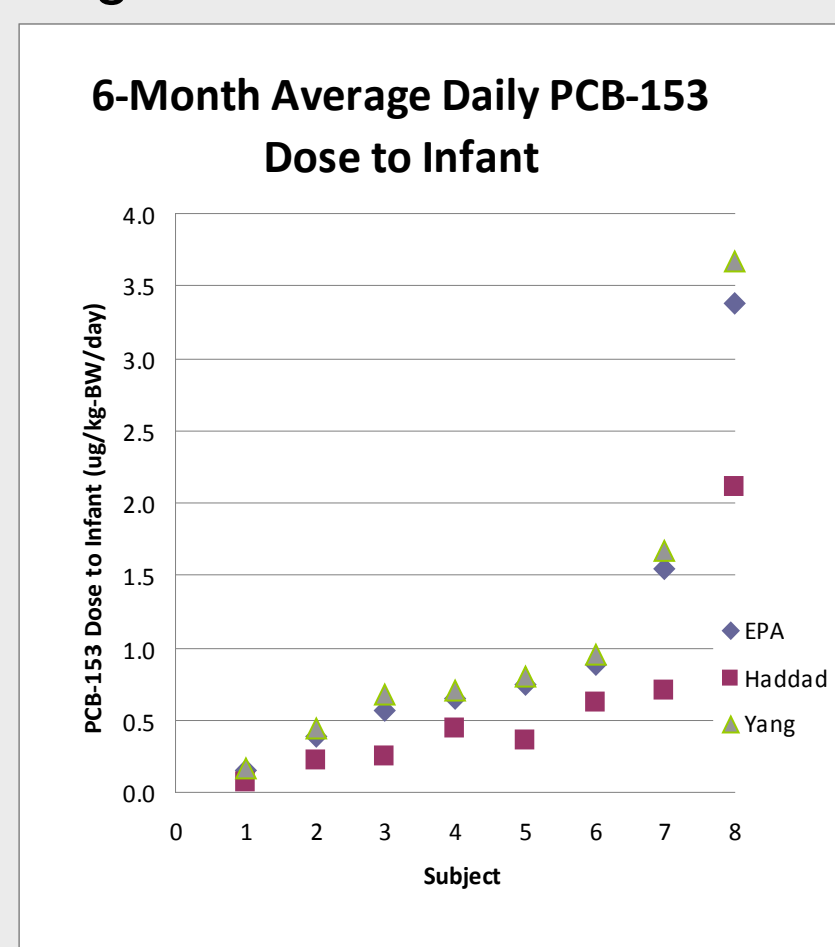
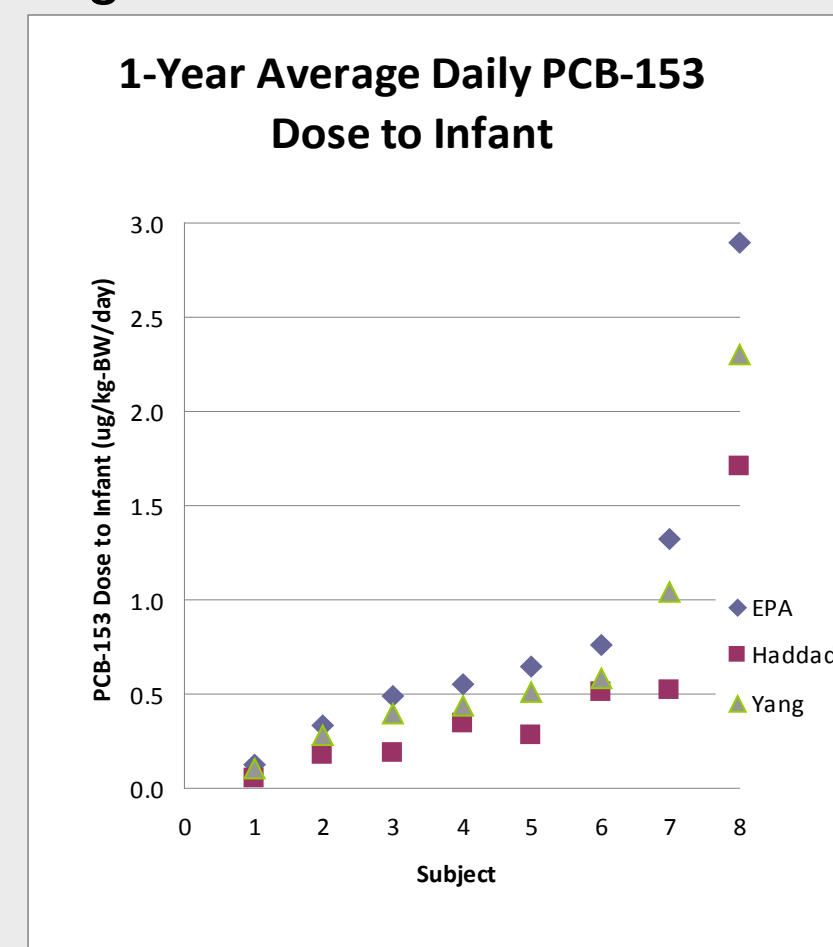


Figure 4



The three models produced simulated milk concentrations that were similar within a factor of 2. Milk concentrations simulated using the Haddad model correlate well with observed milk concentrations for the same individuals ($R = 0.96$, $n = 75$) [1]. Modeled doses to infants are also similar within a factor of 2. Milk concentrations and doses shown represent averaged values over the 6 or 12 month period.

Breast feeding is still the healthiest food source for infants and none of the information presented here should be used to dissuade women from breast feeding. The public health intervention suggested here is to further reduce the mother's exposure to environmental contaminants and to do so at an earlier age.

Figure 5

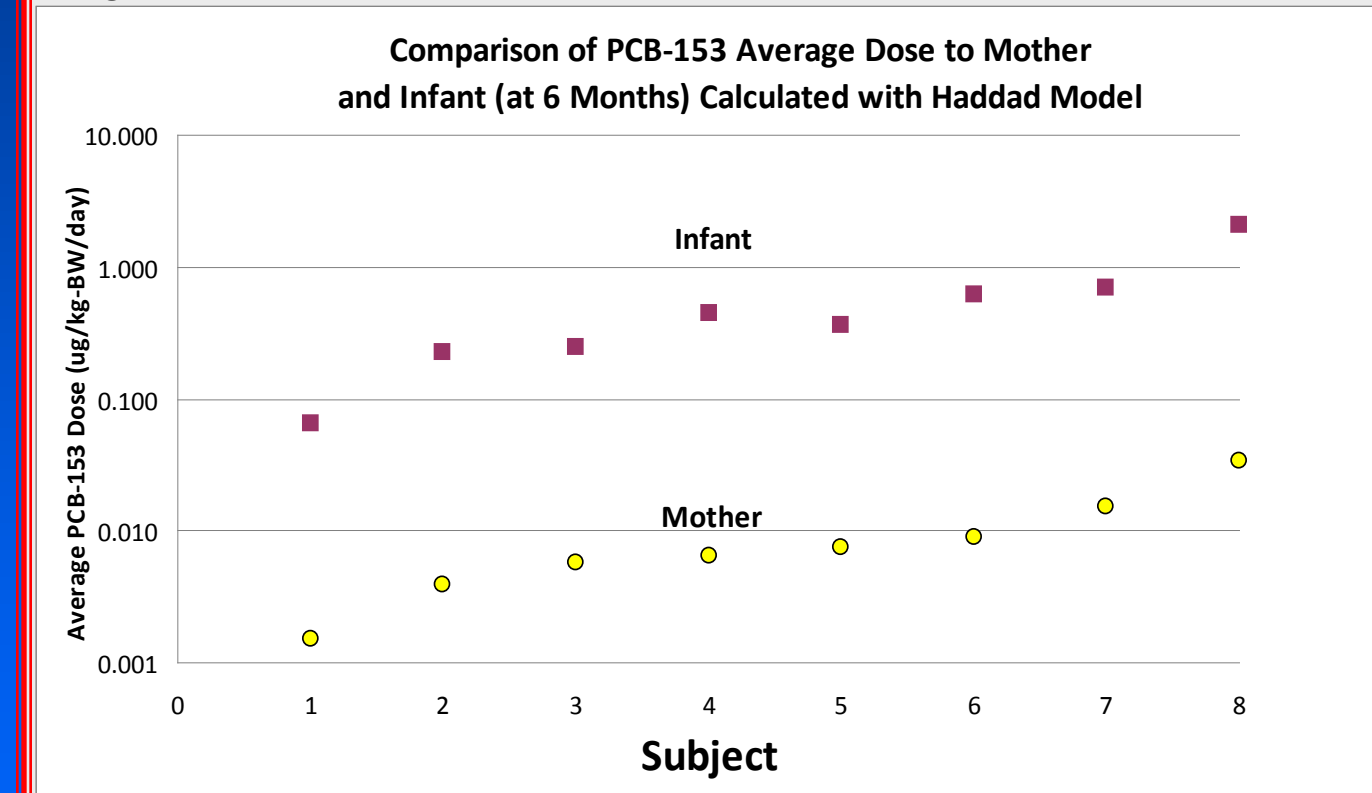
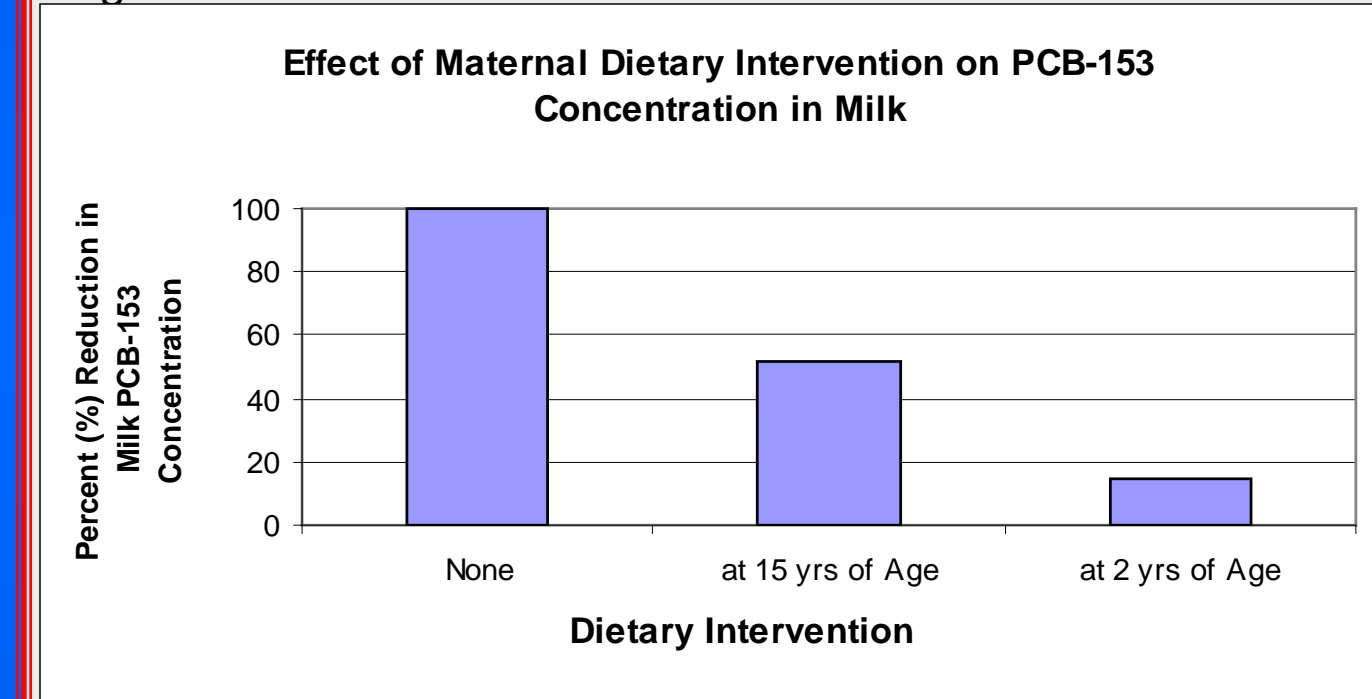


Figure 6

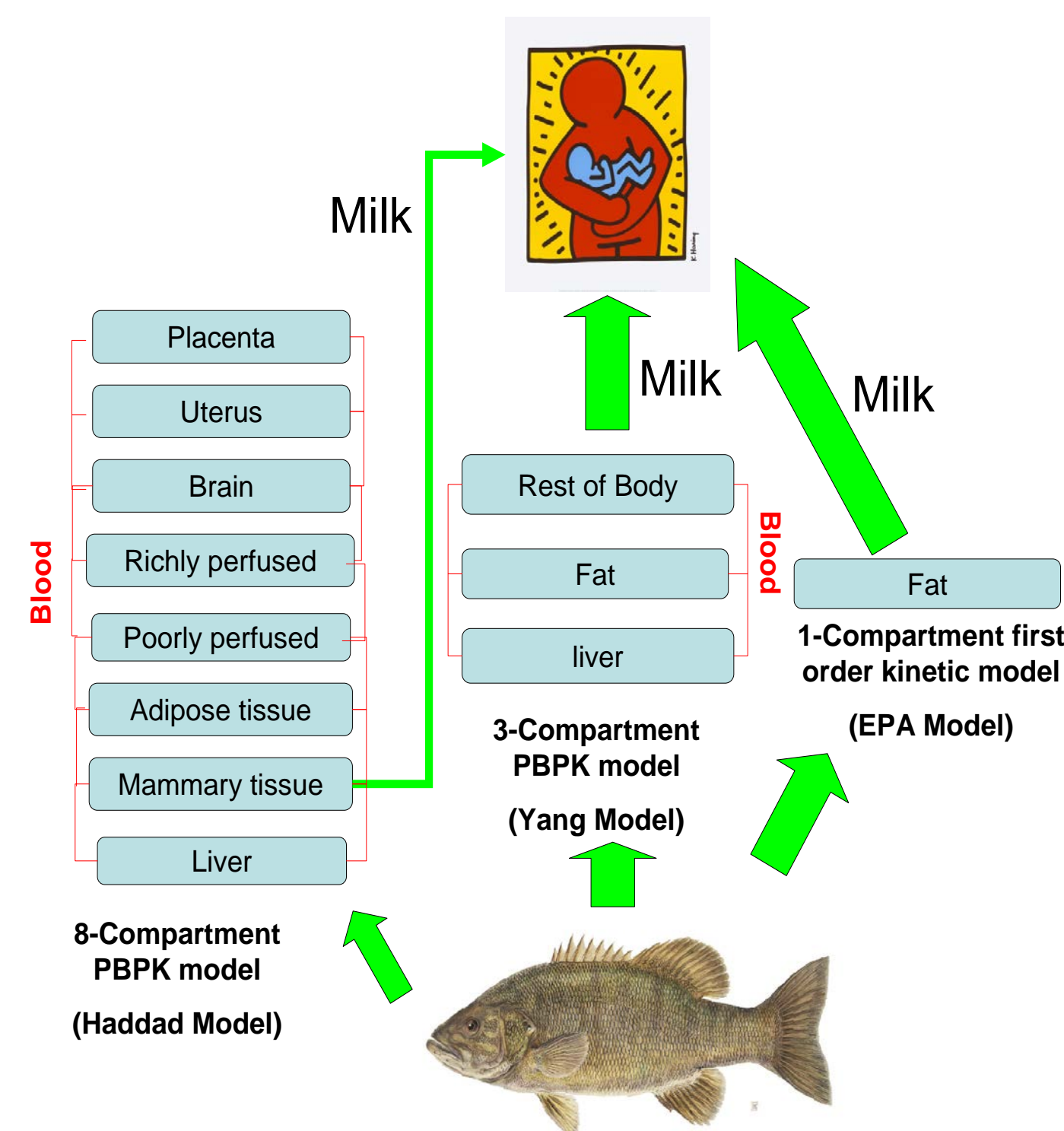


Conclusions

- Estimated milk concentrations can be used to calculate oral dose to infants via human milk.
- These 3 models compared favorably and suggest that the EPA model may be the simplest and sufficiently health-protective model for use in risk assessment and fish advisory formulation.
- All 3 models suggest that the average daily dose of PCB-153 to the infant during the nursing period is approximately 2 orders of magnitude higher than the lifetime average daily dose to the mother.
- Models indicate that the earlier maternal exposure to PCB-153 is reduced, the greater the benefit to the nursing infant.

References

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2. Redding, L.E., et al., *Population physiologically-based pharmacokinetic modeling for the human lactational transfer of pcb 153 with consideration of worldwide human biomonitoring results*. Environmental Health Perspectives, 2008(11519): p. 1-29.
3. Smith, A.H., *Infant exposure assessment for breast milk dioxins and furans derived from waste incineration emissions*. Risk Anal, 1987. 7(3): p. 347-53.
4. EPA, *Human Health Risk Assessment Protocol for Hazardous Waste Combustion Facilities*. 2005. (EPA 530-R-05-006).



Methods

- All three models consider eating contaminated fish as the environmental exposure pathway.
- Simulations were run using all three models to calculate the concentration of PCB-153 in milk after 6 and 12 months of breast feeding (See Fig. 1 and 2).
- Simulations also calculated average daily dose to infants via nursing (See Fig. 3 and 4).
- All three models started using maternal average daily doses for 8 individual Inuit women.
- Maternal average daily doses were back-calculated from measured blood concentrations using the Haddad model.